Registry No.—**1a,** 53052-87-2; **1b,** 53052-91-8; **2a,** 53016-36-7; **2b,** 53052-90-7; **2b** 4*R*-epimer, 53052-89-4; **3a,** 53684-32-5; **4a,** 53053-33-1; **4b,** 53053-35-3; **5a,** 53053-36-4; **5a** trifluoroacetoxy derivative, 29755-34-8; **5b,** 53053-37-5; **6a,** 1035-77-4; **6b,** 3625-82-9; **7a,** 1624-62-0; **7b,** 848-04-4; **8a,** 15375-29-8; **9a,** 53776-51-5; **10a,** 3907-67-3; **11a,** 6702-61-0; **12a,** 6733-79-5; *m*-methoxybenzyl chloride, 824-98-6.

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Synthesis of 9,11-Secoestradiol 3-Methyl Ether

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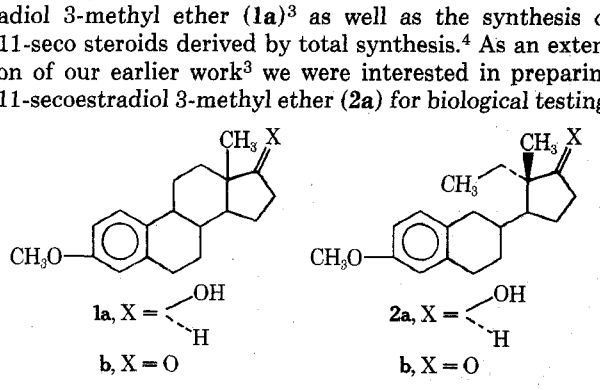
Received October 9, 1974

Estradiol 3-methyl ether (**1a**) is known to possess both estrogenic and antifertility activity. In an attempt to enhance the antifertility activity and/or diminish the estrogenic activity 9,11-secoestradiol 3-methyl ether (**2a**) has been prepared via a seven-step sequence starting with **1a.** Compound **2a** had weak estrogenic and antifertility activity with no appreciable separation of activities.

Several articles dealing with 9,11-seco steroids have appeared in the recent literature. Crossley and Dowell[1] reported the synthesis of 9,11-secoprogesterone in an attempt to prepare a derivative having modified progestational activity. Brain and coworkers[2] prepared a series of 9,11-seco steroids having both the A and B rings aromatic via total synthesis. We have previously reported the synthesis of optically active 9,11-seco steroids derived from estradiol 3-methyl ether (**1a**)[3] as well as the synthesis of 9,11-seco steroids derived by total synthesis.[4] As an extension of our earlier work[3] we were interested in preparing 9,11-secoestradiol 3-methyl ether (**2a**) for biological testing.



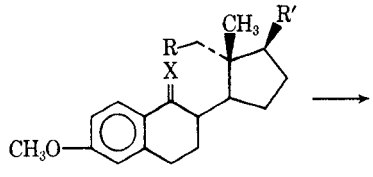
Since estradiol 3-methyl ether (**1a**) is known to possess both estrogenic[5] and antifertility[6] activity, we had hoped that cleavage of the 9,11 bond would enhance the antifertility activity, thereby leading to a greater separation of activities via the "entropy effect."[7]

The key intermediate in our previous series, 17β-hydroxy-3-methoxy-9-oxo-9,11-secoestra-1,3,5(10)-trien-11-oic acid 17-acetate (**3a**), appeared to be an ideal starting material for the synthesis of **2a.** Compound **3a** was prepared by the procedure of Cambie[8] and was purified by column chromatography. The homogeneity of **3a** was established by NMR and thin layer chromatography (TLC). The nmr spectrum of **3a** exhibited sharp singlets at δ 1.08 for the C-18[9] methyl and 1.97 for the acetoxy methyl. If compound **3a** had undergone partial epimerization at C-8 during its preparation, one would expect that the C-18 methyls and/or the acetoxy methyls of the two epimers would have different field positions in the NMR. The only resonances attributable to the C-18 methyl and the acetoxy methyl are the sharp singlets previously mentioned. The homogeneity of **3a** was further confirmed by examining the fully proton decoupled ^{13}C NMR spectrum which contained 20 sharp resonances.[10] If the compound had been a mixture of isomers, some of the carbon atoms would have been nonequivalent and more than 21 peaks would have been observed in the spectrum. Since it is highly unlikely that **3a** had undergone complete epimerization at C-8 during the ring cleavage reaction, we conclude that the stereoconfiguration at C-8 is the same as that in estradiol 3-methyl ether.

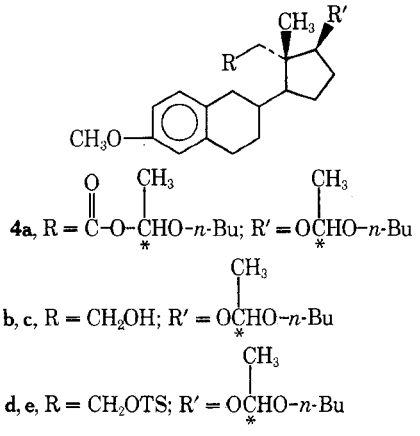
In the synthesis of 9,11-secoprogesterone,[1] the 9-keto and the 11-carboxy functions were removed concurrently by successively reducing each to the corresponding alcohol,

converting the resultant diol into a dimesylate, and displacing the mesylate groups with lithium aluminum hydride. In the synthesis of **2a** we chose to accomplish this series of transformations in a stepwise manner (Scheme I).

Scheme I



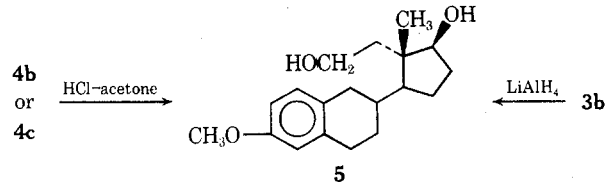
3a, R = COOH; R′ = OAc; X = O
b, R = COOH; R′ = OAc; X = H_2
c, R = COOH; R′ = OH; X = H_2



4a, R = C(=O)-O-CHO-*n*-Bu; R′ = OCHO-*n*-Bu
b, c, R = CH_2OH; R′ = OCHO-*n*-Bu
d, e, R = CH_2OTS; R′ = OCHO-*n*-Bu

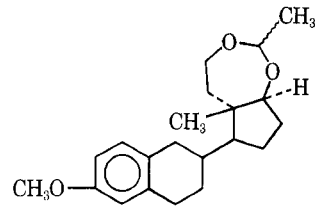
The ketone function at C-9 in compound **3a** was cleanly removed by hydrogenolysis over palladium-on-carbon in ethanol at 50°. In an attempt to determine whether epimerization occurs at C-8 during the reduction compound **3a** was subjected to the reaction conditions in the absence of hydrogen. The ir and NMR spectra, as well as the optical rotation, of the recovered material were virtually identical with that of **3a**, indicating that the compound does not epimerize at C-8 prior to reduction. The fact that a chromatographically homogeneous product, **3b**,[11] was isolated in 78% yield further indicates that epimerization does not occur during the reduction. Although the possibility of complete epimerization occurring during the reduction cannot be ruled out on the basis of our experiments, we feel that such a possibility is highly unlikely.

The conversion of **3b** into **2a** was relatively straightforward. Hydrolysis of **3b** with methanolic KOH afforded the alcohol **3c**. Treatment of **3c** with butyl vinyl ether gave **4a** which reacted in situ with lithium aluminum hydride to afford a pair of diastereomeric butyl vinyl ether derivatives **4b,c** which were separable by column chromatography. Upon hydrolysis, **4b** and **4c** afforded the same diol **5**,[12]



thereby indicating that **4b** and **4c** were isomeric at the newly introduced chiral center resulting from the reaction of the 17β-hydroxy group with butyl vinyl ether.

Treatment of the mixture of **4b,c** with *p*-toluenesulfonyl chloride afforded the tosylates **4d,e** which were used without further purification for the next step. The synthesis of



6

2a was completed by displacing the tosylate group with lithium aluminum hydride followed by acid hydrolysis of the protecting group at C-17. A small amount of an impurity believed to be the cyclic acetal **6** was isolated during the purification of **2a**. Compound **6** is presumed to arise via loss of *n*-butyl alcohol from **4b,c** during the formation of **4d,e**.

Conversion of **2a** into 9,11-secoestrone 3-methyl ether (**2b**) by treatment with Jones reagent further suggests that the assigned structure of **2a** is correct. We speculated that if **2a** has the same stereochemistry as estradiol 3-methyl ether (**1a**), then the difference in molecular rotations[13] between **2a** and **2b** should be of the same magnitude and direction as the difference between the rotations of **1a** and estrone 3-methyl ether (**1b**).[14] The molecular rotations for **1a** and **1b** are +220 and +437, respectively. Therefore, the expected value for **2b** would be 217 more than the value of +193 for **2a**. The observed value of +423 for compound **2b** is in excellent agreement with the predicted value of +410. However, since cleavage of the 9,11 bond of the steroid nucleus gives rise to free rotation about the 8,14 bond, application of the "method of molecular-rotation differences" may not be entirely valid in this instance and our results may indeed be only coincidental.

Compound **2a** was found to have 0.30% the estrogenic activity[5] of estradiol 3-methyl ether (**1a**). A comparison of the antifertility activities[6] revealed that **2a** had an ED_{50} of 450 μg vs. an ED_{50} of 2.5 μg for **1a**. Hence, cleavage of the 9,11 bond resulted in a marked reduction of the estrogenic and antifertility activities. Little, if any, separation of activities was achieved.

Experimental Section

Melting points were determined on a Fisher-Johns melting block and are uncorrected. Infrared spectra were recorded on a Beckman IR-12 grating spectrophotometer. NMR spectra were obtained in $CDCl_3$ on a Varian A-60 or T-60 or XL-100 spectrometer using tetramethylsilane as internal standard. Specific rotations were obtained in chloroform (*c* 1.0) using a Perkin-Elmer (Model 141) polarimeter. Elemental analyses were performed by the microanalytical group at Searle Laboratories.

Purification of 3a. A sample of **3a** prepared by the procedure of Cambie[8] was chromatographed on SilicAR CC-4 using benzene and EtOAc as eluents. Pure **3a** was obtained in the 20 and 40% EtOAc fractions and was recrystallized from benzene–Skellysolve B to give a white solid: mp 148–150°; $[\alpha]^{25}D$ −13°; ir (KBr) 1745 [OC(=O)CH_3], 1730 (COOH), and 1680 cm^{-1} (conjugated ketone); NMR δ 1.10 (s, CH_3), 1.98 [s, OC(=O)CH_3], 3.86 (s, OCH_3).

(1*S*,2*S*,2′*R*,5*S*)-2-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-5-hydroxy-1-methylcyclopentaneacetic Acid Acetate (3b). A solution of **3a** (4.54 g, 12.1 mmol) in 250 ml of EtOH was hydrogenated over 5% Pd-on-carbon (0.5 g) at 50° for 72 hr in a Parr shaker. The solution was filtered and the solvent was removed in vacuo to give 4.37 g of a yellow oil which crystallized upon standing. The product was chromatographed on 90 g of SilicAR CC-4 to give **3b** in the 10% EtOAc–90% benzene fractions. Recrystallization from EtOAc–Skellysolve B gave **3b** (3.40 g, 78%): mp 125–127°; $[\alpha]^{25}D$ +50°; NMR δ 1.03 (s, CH_3), 2.02 [s, OC(=O)CH_3], 3.76 (s, OCH_3).

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.64; H, 7.84.

Control Experiment on 3a. A solution of **3a** (0.454 g, 1.21 mmol) in 25 ml of EtOH containing 0.050 g of Pd-on-carbon was heated at 50° for 72 hr under nitrogen. The solution was filtered

and the solvent was removed in vacuo to give 0.450 g of an oil which crystallized upon standing. The ir and NMR spectra as well as the optical rotation on the recovered material were virtually identical with those of **3a:** $[\alpha]^{22}D$ −11°; NMR δ 1.10 (s, CH_3), 1.99 [s, $OC(=O)CH_3$], 3.87 (s, OCH_3).

(1*S*,2*S*,2′*R*,5*S*)-2-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-5-hydroxy-1-methylcyclopentaneacetic Acid (3c). A solution of **3b** (3.33 g, 9.25 mmol) in 50 ml of CH_3OH was treated with a solution of KOH (3.00 g, 53.5 mmol) in 15 ml of water, and the solution was refluxed for 2 hr. The solution was diluted with 250 ml of water, filtered, and acidified with hydrochloric acid. The solid which formed was collected and thoroughly washed with water. Recrystallization from EtOAc–Skellysolve B gave **3c** (2.65 g, 90%): mp 141.5–142.5°; $[\alpha]^{23}D$ +65°; NMR δ 0.97 (s, CH_3), 3.76 (s, OCH_3).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.35; H, 8.35.

Conversion of 3c into 4b,c. A solution of **3c** (2.57 g, 8.09 mmol) in 15 ml of THF was treated with *n*-butyl vinyl ether (1.70 g, 17.0 mmol) and 3 drops of a 10% solution (v/v) of methanesulfonic acid in THF. After stirring at room temperature for 4 hr, no further reaction could be detected by TLC (20% EtOAc–80% benzene). The crude mixture was added dropwise to a stirred suspension of $LiAlH_4$ (0.500 g, 13.2 mmol) in 20 ml of THF and the mixture was stirred at room temperature for 24 hr. The mixture was carefully hydrolyzed by the dropwise addition of 2.0 ml of 5% NaOH solution. The mixture was diluted with 50 ml of ether and filtered. The inorganic salts were thoroughly washed with ether and the combined organic phases were concentrated in vacuo. TLC (20% EtOAc–80% benzene) indicated the presence of two compounds, **4b,c** in a ratio of 1:1 along with a lesser amount of **5.** The crude mixture was chromatographed on 90 g of SilicAR CC-7 using EtOAc and benzene as eluents and taking 40-ml fractions. Compound **4b** (1.27 g, 39%) was obtained pure in the 2% and early 5% EtOAc–benzene fractions. A mixture of **4b,c** (0.513 g, 16%) was obtained in the later 5% and early 10% EtOAc–benzene fractions. Compound **4c** (1.07 g, 33%) was obtained pure in the later 10 and 20% EtOAc–benzene fractions. Compound **5** (0.247 g, 8%) was obtained in the 100% ethyl acetate fractions. Recrystallization from benzene afforded 0.170 g of **5,** mp 151–152°, $[\alpha]^{23}D$ +58°. Compound **5** was virtually identical with an authentic sample prepared from **3b.**

(1*S*,2*S*,2′*R*,5*S*)-2-(1,2,3,4-Tetrahydro-6-methoxy-2-naphthyl)-5-hydroxy-1-methylcyclopentaneethanol (5). A solution of **3b** (0.780 g, 2.17 mmol) in ether (10 ml)–THF (5 ml) was added dropwise to a stirred slurry of $LiAlH_4$ (0.420 g, 11.1 mmol) in 400 ml of ether, and the mixture was stirred at room temperature for 18 hr. The mixture was hydrolyzed by the dropwise addition of 1.7 ml of 5% NaOH solution. The mixture was diluted with 40 ml of CH_2Cl_2 and filtered. The solvent was removed in vacuo to give a white solid which was recrystallized from benzene–Skellysolve B to give **5** (0.585 g, 89%): mp 151–153°; $[\alpha]^{24}D$ +62°; NMR δ 0.87 (s, CH_3), 3.74 (s, OCH_3).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.91; H, 9.27.

Hydrolysis of 4b. A solution of **4b** (0.136 g, 0.336 mmol) in 5 ml of acetone and 1 ml of water was treated with 4 drops of concentrated HCl, and the solution was stirred for 30 min. The product was precipitated by adding 15 ml of water and saturating the solution with NaCl. The product was collected, air dried, and recrystallized from benzene–Skellysolve B to give **5** (0.0681 g, 67%), mp 151.5–153.5°, $[\alpha]^{23}D$ +63°. The compound was virtually identical with an authentic sample of **5** prepared from **3b.**

Hydrolysis of 4c. A sample of **4c** (0.107 g, 0.290 mmol) was treated in the same manner as **4b** to give a product which was recrystallized from benzene–Skellysolve B to give **5** (0.0454 g, 52%), mp 151–153°, $[\alpha]^{23}D$, +61°. The compound was virtually identical with an authentic sample of **5** prepared from **3b.**

Conversion of 4b,c to 4d,e. A solution of **4b,c** (2.59 g, 6.40 mmol) in 20 ml of pyridine was treated with *p*-toluenesulfonyl chloride (2.46 g, 12.8 mmol) and the reaction mixture was placed in a refrigerator for 42 hr. The mixture was poured onto 200 ml of water, stirred for 15 min, and extracted with ether. The extracts were dried over anhydrous Mg_2SO_4 and filtered. The solvent was removed in vacuo to give 3.83 g of an oil[15] which was used without further purification.

(1*S*,2*S*,2′*R*,3*S*)-2-Ethyl-2-methyl-3-(1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)cyclopentanol (2a). A solution of **4d,e**[15] (3.83 g, 6.86 mmol) in 30 ml of THF was added dropwise to a stirred suspension of $LiAlH_4$ (2.00 g, 52.8 mmol) in 70 ml of THF and the mixture was refluxed for 18 hr. The mixture was diluted with 50 ml of ether and hydrolyzed by the dropwise addition of 8 ml of a 10% NaOH solution. The solution was filtered and the inorganic salts were thoroughly washed with ether. The organic solvents were removed in vacuo to give 2.61 g of an oil which was dissolved in 50 ml of acetone and 10 ml of water and treated with 1 ml of concentrated HCl. After stirring for 90 min, the mixture was diluted with 500 ml of water and extracted with ether. The extracts were dried over anhydrous Mg_2SO_4 and filtered. The solvent was removed in vacuo to give 1.72 g of an oil which was chromatographed on 90 g of SilicAR CC-7 using EtOAc and benzene as eluents and taking 40-ml fractions. Compound **6** (0.087 g, 4%) was obtained in the first few benzene fractions. Compound **2a** (1.29 g, 70%) was eluted with 10% EtOAc–90% benzene. Recrystallization from pentane afforded 1.07 g of **2a:** mp 42–43.5°; $[\alpha]^{25}D$ +67°; NMR δ 0.83 (s, CH_3), δ 0.88 (t, J = 7 Hz, CH_3), 3.77 (s, OCH_3).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.87; H, 9.67.

(2*S*,2′*R*,3*S*)-2-Ethyl-2-methyl-3-(1,2,3,4-tetrahydro-6-methoxy-2-naphthyl)cyclopentanone (2b). A solution of **2a** (0.400 g, 1.39 mmol) in 30 ml of acetone was cooled to 0°, and excess Jones reagent was added dropwise until the orange color persisted for 10 min. The excess reagent was destroyed by the dropwise addition of isopropyl alcohol and the reaction mixture was diluted with 100 ml of water and extracted with ether. The extracts were dried over anhydrous Mg_2SO_4 and filtered. Solvent removal gave a yellow oil which was chromatographed on 30 g of SilicAR CC-7 using Skellysolve B and benzene as eluents. The product was eluted in the benzene fractions and the solvent was removed in vacuo to give 0.337 g of an oil which crystallized upon standing. Recrystallization from pentane afforded **2b** (0.300 g, 75%): mp 77.5–79.5°; $[\alpha]D$ +148°; NMR δ 0.96 (s, CH_3), 0.74 (t, J = 7 Hz, CH_3), 3.80 (s, OCH_3).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.89; H, 9.25.

Acknowledgment. The authors gratefully acknowledge the technical assistance of Mr. Bipin Desai, Mrs. Karlene Salamon, and Miss Bobbie Coleman in the preparation of some of the seco steroids, of Mr. William Selby and his staff for optimizing the yield in the hydrogenolysis reaction, of Mr. Wally Pautsch and his staff in the biological evaluation of the compounds, and of Miss Patricia Green for interpreting and assigning the resonances in the noise decoupled ^{13}C NMR spectrum of **3a.**

Registry No.—**2a,** 53940-71-9; **2b,** 53940-72-0; **3a,** 1247-46-7; **3b,** 53940-73-1; **3c,** 53940-74-2; **4b,** 53940-75-3; **4c,** 54003-03-1; **4d,** 53940-76-4; **4e,** 53990-65-1; **5,** 53940-77-5.

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(8) R. C. Cambie and T. D. R. Manning, *J. Chem. Soc. C,* 2603 (1968).
(9) The steroid numbering system has been used throughout the text of this paper for convenience.
(10) Since compound **3a** contains 21 carbons, the presence of only 20 resonances in the decoupled spectrum indicates that two of the carbon atoms, most likely C-6 and C-7, are magnetically equivalent.
(11) Compound **3b** was purified by column chromatography (see Experimental Section) to remove trace amounts of unreacted **3a** as well as trace amounts of a more polar material believed to be the 9-hydroxy intermediate.
(12) An authentic sample of **5** was prepared by treating **3b** with lithium aluminum hydride.
(13) The "method of molecular-rotation differences" has had many successful applications in the steroid field. For a summary, see D. H. R. Barton and W. Klyne, *Chem. Ind. (London),* 755 (1948).
(14) Samples of **1a** and **1b** were obtained from Searle Chemicals Inc. The specific rotations are $[\alpha]^{25}D$ +77° and $[\alpha^{25}D$ +154°, respectively.
(15) The sample contained a small amount of pyridine. Theory requires 3.57 g, 6.40 mmol.